Towards more robust estimates of the transmissibility of *Chlamydia trachomatis*

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Abstract

There is a lack of a common concept on how to estimate transmissibility of *Chlamydia trachomatis* from cross-sectional sexual partnership studies. Using a mathematical model that takes into account the dynamics of chlamydia transmission and sexual partnership formation, we report refined estimates of chlamydia transmissibility in heterosexual partnerships.

Summary

This study provides improved estimates of the transmissibility of Chlamydia trachomatis in heterosexual partnerships, using a mathematical model that considers the dynamics of chlamydia transmission and sexual partnership formation.

Knowledge about the transmissibility of *Chlamydia trachomatis* (chlamydia) is important for health professionals to be able to give accurate information to their patients and for those investigating and implementing preventive interventions.[1] Estimates of transmission probabilities are needed in research studies to parameterize mathematical and computational models, which are used to study the transmission dynamics of chlamydia and the impact of public health interventions such as screening programs.[2] Chlamydia is the most commonly diagnosed bacterial sexually transmitted infection in many developed countries. Prevalence is high with more than 2 million infected persons per year in the USA alone.[3] It is, however, difficult to obtain reliable estimates of chlamydia transmissibility from observational epidemiological studies.

Empirical estimates of the transmissibility of chlamydia have usually been based on data about the proportions of concordant and discordant pairs that are infected or uninfected with chlamydia.[4] Katz proposed an original approach for analyzing such couple data.[5] The expected numbers of concordant and discordant couples before transmission takes place can be calculated if it is assumed that all couples in the population with at least one infected individual have the same probability of observation and that sexual partnership formation is independent of infection status. After sexual partnerships have formed, transmission can happen in discordant partnerships resulting in a higher proportion of couples where both partners are positive. Using data from heterosexual couples attending a sexually transmitted diseases (STD) clinic in Indianapolis, Katz estimated the probabilities that transmission has occurred within a couple at 0.395 from men to women and 0.323 from women to men. There are two major problems with this approach, however. First, the infection status of the couples is observed during the partnership and not at the end so the estimated transmission probabilities do not represent the per partnership transmission probability; this frequently used concept implies the probability of transmission by the end of the partnership. Second, it does not take into account the natural history of chlamydia infection where spontaneous clearance and re-infection within sexual partnerships can occur.[6] These additional complexities need to be considered because different assumptions about the infectious duration and re-infection in sexual partnerships can affect the prevalence of chlamydia.[7,8]

In this study, we apply a mathematical model to data from a cross-sectional partnership study that has frequently been used as the source of estimates for chlamydia transmissibility.[9] Mathematical models are a tool for explicitly describing the dynamics of sexual partnership

formation and transmission of chlamydia infection. The pair model framework has proven useful for describing the transmission of chlamydia and other STIs.[8,10–12] The model considers the formation of sexual partnerships or pairs (P) and their dissolution into singles (X). Quinn et al. studied heterosexual couples attending two STD clinics in Baltimore.[9] There were comparable numbers of discordant couples where either the woman or man was infected, so we made the simplifying assumption that the prevalence and the natural history of chlamydia infection were the same in women and men. Assuming a SIS (susceptible-infected-susceptible) structure, the pair formation and chlamydia transmission can be described by the following set of ordinary differential equations:

$$
\begin{aligned}
\frac{dX_S}{dt} &= -\rho X_S + \gamma X_I + 2\sigma P_{SS} + \sigma P_{SI}, \\
\frac{dX_I}{dt} &= -\rho X_I - \gamma X_I + 2\sigma P_{II} + \sigma P_{SI}, \\
\frac{dP_{SS}}{dt} &= \frac{1}{2}\rho\frac{X_S^2}{X} + \gamma P_{SI} - \sigma P_{SS}, \\
\frac{dP_{SI}}{dt} &= \rho\frac{X_S X_I}{X} - f\beta P_{SI} + 2\gamma P_{II} - \gamma P_{SI} - \sigma P_{SI}, \\
\frac{dP_{II}}{dt} &= \frac{1}{2}\rho\frac{X_I^2}{X} + f\beta P_{SI} - 2\gamma P_{II} - \sigma P_{II}.
\end{aligned}
$$

The infection status is represented by the indices S and I for being susceptible or infected, respectively. Singles X seek partners at rate ρ resulting in sexual partnerships with a concordant (P_{SS} and P_{II}) or discordant (P_{SI}) chlamydia infection status. The duration of sexual partnerships and infection are exponentially distributed with a mean duration of $1/\sigma$ and $1/\gamma$, respectively. Within discordant partnerships, couples engage in heterosexual intercourse at rate f and transmission happens with probability β per sex act. The per partnership transmission probability p is defined as the probability that an infected individual transmits chlamydia to his or her susceptible partner before the infection is spontaneously cleared or the partnership breaks up ($p = f\beta/(\sigma + \gamma + f\beta)$).

We assumed that chlamydia infection in the population had approached steady-state, i.e., all derivates can be set to zero. We then used maximum likelihood estimation (MLE)[13] to fit the model to the data from the study by Quinn et al.[9] The study contains information about chlamydia infection status and sexual activity in 494 heterosexual couples. The study reported 53 concordant chlamydia positive, 48 discordant and 393 concordant negative couples. The median number of sex partners in the last 6 months was reported to be 1 in females and 2

in males. In the model, we account for a skewed distribution and vary the mean number of partners during the previous 6 months for individuals in a partnership at steady-state between 1.5 and 3. The median number of episodes of sexual intercourse in the preceding 30 days was reported to be 6, so we assumed one sex act every 5 days. Due to uncertainties in the duration of sexual partnerships and infections, we generated 1000 parameter combinations by sampling the mean partnership duration from a uniform distribution between 1 week and the maximal duration that is consistent with the assumed number of partners in the last 6 months, and the infectious duration from a uniform distribution between 6 and 12 months.[7] Note that infectious durations of more than 12 months resulted in poor descriptions of the data.

The pairs in the model represent the couples from the study by Quinn et al.[9]. The singles can be interpreted as the population from which they are drawn. Assuming that the test data are binomially distributed, we fitted the model to the overall positivity of all individuals in couples (154 of 988) and to the positivity of partners of index patients that are either chlamydia positive (53 of 77) or negative (24 of 417). Using the function mle from the R software environment for statistical computing,[14] we estimated the per sex act transmission probability β from which we also derived the per partnership transmission probability p. Estimates that resulted in per sex act transmission probabilities of more than 100% or low goodness of fit based on the Akaike information criterion (AIC)[15] were excluded.

We obtained model estimates of the per partnership transmission probability for different values of the number of partners during the last 6 months (Fig. 1A). Higher number of partners resulted in lower estimates of the per partnership transmission probability. However, partner numbers of 3 or more during the last 6 months resulted in poor fits to the data. We therefore consider 2 partners during the last 6 months as our baseline scenario for which the median of the estimated per partnership transmission probability is 55.5% (interquartile range (IQR): 49.2% – 62.5%). The estimates of the per sex act transmission probability seemed to be less affected by the assumed number of partners in the last 6 months (Fig. 1B). Most values were around 10% with the median of the baseline scenario at 9.5% (IQR: 6.0% – 16.7%).

Our estimated range of chlamydia transmission probabilities in heterosexual partnerships is higher than the baseline values reported by Katz.[5] This is expected because we report the probability of transmission taking place by the end of a partnership. The additional assumption that chlamydia can be cleared spontaneously also results in higher estimates of the transmission probability. Interestingly, our estimate is lower than what others have concluded from the same

data.[9] Seventy per cent of female and 68% of male partners were infected with chlamydia if their sexual partner was also chlamydia-positive. These values have often, but incorrectly, been interpreted as the per partnership transmission probabilities.[16,17] However, the direction of transmission cannot be reliably determined from these raw percentages.[6] This discrepancy illustrates the importance of taking into account the natural history of chlamydia infection and the dynamics of sexual partnership formation in estimating transmissibility from data of chlamydia-positivity in couples.

The estimates of the per sex act transmission probability for chlamydia are consistent with those obtained or used in other modeling studies[18–20]. While the estimates are lower than for *Neisseria gonorrhoeae*,[4,21] they are considerably higher than the per heterosexual sex act transmission probability for HIV.[22,23] Our estimates of the per sex act transmission probability are limited by the lack of information on the number of unprotected episodes of heterosexual intercourse in the couples. While one episode of intercourse every 5 days on average is in good agreement with population-based data of sexual activity,[24,25] the proportion of unprotected episodes is unknown. An additional limitation is that we could not investigate differences between women and men. Different female-to-male and male-to-female transmission probabilities and a higher proportion of symptomatic cases in men could result in sex-specific differences in the transmission and prevalence of chlamydia. As already noted, however, the data from Quinn et al. showed a strikingly similar chlamydia positivity pattern between women and men.[9] Ultimately, our estimates are derived from a single study population. While this ensures consistency of our results, the per partnership transmission probability might differ in the general population where partnership durations might be longer than in the study population.

The framework described here does not take into account natural variability in chlamydia transmission. For example, spontaneous resolution of chlamydia could confer a certain degree of immunity,[26] resulting in heterogeneity of susceptibility and transmissibility in a population. Tu et al. present a promising Bayesian framework using detailed longitudinal individual level data about chlamydia infection status and the type and frequency of sexual intercourse in women.[20] If such longitudinal data sets were matched to the women's male partners' infection status and sexual behavior, more detailed investigations of sex differences in chlamydia transmissibility and its heterogeneity could be performed. In summary, we report the expected ranges of the average per partnership and per sex act chlamydia transmission probability. Fur-

ther efforts will be needed to investigate the between-individual heterogeneity in susceptibility and transmissibility of chlamydia.

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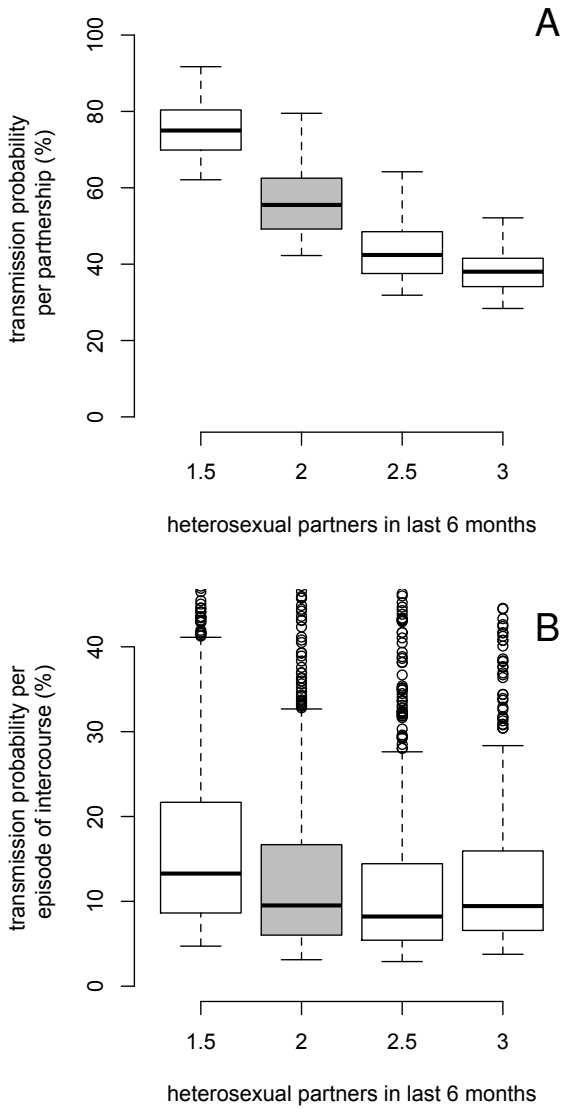

Figure 1: Estimated transmission probabilities for different values of the number of partners in the last 6 months. (A) Per partnership transmission probability of chlamydia. (B) Per sex act transmission probability of chlamydia. Each boxplot represents estimates from 1000 different parameter combinations. The baseline scenario, where it is assumed that individuals in a partnership at steady-state have on average 2 heterosexual partners during the previous 6 months, is in gray. It is assumed that individuals have one episode of heterosexual intercourse every 5 days.